SYNTHESIS OF 2-t-BUTYL-5-HYDROXYPYRIMIDINE VIA HYDROLYSIS OF 2-t-BUTYL-5-HALOPYRIMIDINES

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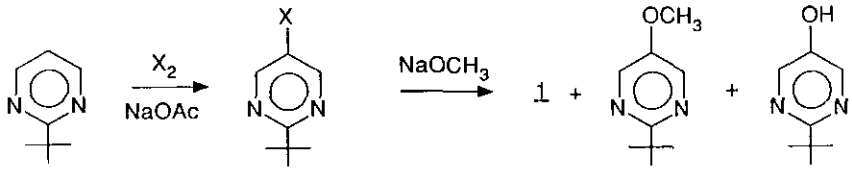
Abstract - The hydrolysis of 2-t-butyl-5-halopyrimidine (halogen = bromine or chlorine) with sodium methoxide in methanol yields 2-t-butyl-5-hydroxypyrimidine. The side reaction product, 2-t-butylpyrimidine, is substantially reduced, especially in the case of the bromo derivative, with catalytic amounts of elemental sulfur.

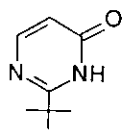
The 2-alkyl-5-hydroxypyrimidines are valuable intermediates for the synthesis of pyrimidyl phosphate insecticides.[1] Recently, we published the synthesis of 2-alkylpyrimidines via dehydrogenation of the 2-alkyl-1,4,5,6-tetrahydropyrimidines.[2] Since halogenation of alkylpyrimidines to alkyl-5-halopyrimidines is well documented in the literature,[3] the successful hydrolysis of the halo derivatives represents an attractive route to the desired 2-alkyl-5-hydroxypyrimidines. This paper describes a method for the hydrolysis of the 2-alkyl-5-halopyrimidines, specifically the 2-t-butyl derivative.

The 5-chloro and 5-bromo derivatives of 2-t-butylpyrimidine (2) were prepared by halogenation of 2-t-butylpyrimidine (1) in acetic acid with sodium acetate buffer.



1 2 (a, X = Br) (b, X = Cl) 3 4

Exploratory experiments on the hydrolysis of 2a with sodium hydroxide in either ethylene glycol or dimethyl sulfoxide were not encouraging; but the use of methanol and sodium methoxide under pressure at 135-160°C gave good conversions of the starting material to a mixture of the desired pyrimidinol, 4, and the reduced pyrimidine, 1. The intermediate methoxypyrimidine 3 is also produced in significant amounts either at short reaction times or lower temperatures. (See Table 1.) An attempt to replace sodium methoxide with sodium hydroxide gave additionally poor yields of 4 in addition to 10-15% of the 2-t-butyl-3,4-dihydro-4-oxo-pyrimidine, 5. Presumably, 5 is formed via an alternative



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mechanism involving a benzyne intermediate. The formation of the reduced pyrimidine 1 may occur by a radical anion mechanism as discussed by Bunnett.[4] The mechanism does not define either the initiation step or the termination step but does suggest a means of inhibiting the reduction. Inhibitors that are better electron acceptors than the aryl halide and block dehalogenation

$$R\cdot + CH_3OH \rightarrow RH + \cdot CH_2OH$$

$$CH_3O^- + \cdot CH_2OH \rightleftharpoons CH_3OH + \cdot CH_2O^-$$

$$\cdot CH_2O^- + HetBr \rightarrow CH_2O + [HetBr]\cdot^-$$

$$[HetBr]\cdot^- \rightarrow Het\cdot + Br^-$$

$$Het\cdot + CH_3OH \rightarrow HetH + \cdot CH_2OH$$

by capturing an electron from $\cdot CH_2O^-$ and thereby are reduced to the inhibitor radical anion which acts as a chain terminator. The results of several inhibitors are summarized in Table 1. As noted for Runs 1 and 2, the hydrolysis of 2a with sodium methoxide in methanol yields approximately 40% of the reduced pyrimidine 1. The addition of either 2-methylpyridine-1-oxide or di-n-butyl disulfide (Runs 3-6) significantly reduces the amount of 1 in the product.

Table 1. Hydrolysis of 2-t-Butyl-5-halopyrimidine*

Run	Moles		Inhibitor	Temp.	Mass	1	3	4
	Halide	Methoxide	(mol %)	(°C)	Balance			
1	2a(0.02)	0.104	0	140	96	45	0	41
2	2a(0.02)	0.104	0	150	106	37	11	58
3	2a(0.02)	0.104	A(10)	152	93	12	12	69
4	2a(0.02)	0.104	A(20)	152	89	12	1	76
5	2a(0.02)	0.104	B(5)	160	104	12	1	91
6	2a(0.02)	0.104	B(10)	160	114	7	1	105
7	2a(0.02)	0.104	C(0.5)	160	111	12	0	99
8	2a(0.02)	0.104	C(1.5)	160	111	10	0	101
9	2a(0.02)	0.104	C(2.5)	155	102	8	2	93
10	2a(0.02)	0.104	C(2.5)	160	116	5	6	106
11	2a(0.02)	0.104	C(2.5)	175	93	8	0	85
12	2a(0.02)	0.104	C(5.0)	165	99	5	0	94
13	2a(0.02)	0.104	C(5.0)	175	102	7	0	95
14	2a(0.02)	0.104	C(7.5)	155	104	4	0	100
15	2b(0.1)	0.300	--	160	100	9	0	91
16	2b(0.1)	0.300	--	170	91	8	0	83
17	2b(0.1)	0.300	C(2.5)	170	89	4	0	85
18	2b(0.1)	0.300	C(2.5)	170	97	4	0	93

A = 2-methylpyridine 1-oxide; B = di-n-butyl disulfide; C = sulfur.

* = Solvent: Methanol (50 ml). Conversion: 100%. Time: 12 h.

From the results in Table 1, the preferred inhibitor is sulfur that at the 2.5-5.0% level reduces the reduction product, 1, to less than 10%. At 7.5% sulfur, the amount of 1 is less than 5%.

If the mechanism proposed by Bunnett is operative, substitution of chlorine for bromine should substantially decrease the amount of reduction during the hydrolysis. The results of Runs 15-18 demonstrate this to be true. Whereas the bromine derivative gave approximately 40% of 1, the hydrolysis of 2b gives less than 10%. Addition of 2.5% sulfur reduces the amount to less than 5%.

In summary, a practical method has been developed for the preparation of 2-alkyl-5-hydroxypyrimidines from either the chloro or bromo precursor. In addition, the use of sulfur has been demonstrated as an effective inhibitor of $S_{RN}1$ reactions that lead to reduced pyrimidine, especially with the bromo derivative.

EXPERIMENTAL

Preparation of 2-t-Butyl-5-bromopyrimidine (2a)

2-t-Butylpyrimidine (25 g, 0.18 mol) was added to glacial acetic acid (125 ml) containing sodium acetate (17.2 g, 0.21 mol). The mixture was heated to 80°C and bromine (32 g, 0.18 mol) was added dropwise maintaining the temperature at 80°C. After 3 h, the reaction was analyzed by gc analysis and found to be about 80% complete. An additional 7 g of bromine was added and the mixture was stirred for an additional 3 h. The reaction mixture was filtered hot and the acetic acid was removed via distribution. The residue was diluted with dichloromethane and washed with water and dilute aqueous potassium carbonate, dried over $MgSO_4$, and the dichloromethane was removed on a Büchi evaporator. The residue was distilled in vacuum (bp 90°, 3 mm) to give the desired 2-t-butyl-5-bromopyrimidine 25.7 g (60%), mp, 50-52°C. Ms m/z: 214 (M^+, calcd for $C_8H_{11}BrN_2$: 214). Nmr ($CDCl_3$) 1.35 (s, 9, $-C(\underline{CH_3})_3$), 8.75 (s, 2, H-5,6).

Preparation of 2-t-Butyl-5-chloropyrimidine (2b)

This material was prepared as described for the bromo derivative in acetic acid-sodium acetate solution at 55°C. Distillation of the crude product gave 2b (75%), bp 122-124°C (100 mm), mp 39-40°C. Ms m/z: 170 (M^+, calcd for $C_8H_{11}ClN_2$: 170). Nmr ($CDCl_3$) 1.35 (s, 9, $-C(CH_3)_3$), 8.68 (s, 2, H-5,6).

Isolation of 2-t-Butyl-3,4-dihydro-4-oxopyrimidine (5)

2-5-Butyl-5-bromopyrimidine (51.6 g, 0.24 mol) was added to a 600 ml Hastelloy C Parr bomb equipped with mechanical stirrer and containing a solution of 40.5 g (1.20 mol) of sodium hydroxide in 350 ml of methanol. The bomb was sealed, heated and stirred for 12 h at 160°C. After cooling, the methanol was removed on a Büchi evaporator. The residue was diluted with water and neutralized to pH 7 with dilute hydrochloric acid. The aqueous solution was extracted twice with dichloromethane. The dichloromethane extract was dried over $MgSO_4$ and the dichloromethane was removed on a Büchi evaporator. The oxo compound was recrystallized from CCl_4 to give product (5.22 g, 14%), mp 146-148°C. Nmr ($CDCl_3$) 1.40 (s, 9, $-C(CH_3)_3$), 6.35 (d, 1, J = 7.0 Hz, H-5), 8.05 (d, 1, J = 7.0 Hz, H-6); ir (CCl_4) ν 1650 (CO). Anal. Calcd for $C_8H_{12}N_2O$: C, 62.30; H, 7.20; N, 18.48. Found: C, 62.15; H, 7.89; N, 18.30.

Isolation of 2-t-Butyl-5-methoxypyrimidine (3)

2-t-Butyl-5-bromopyrimidine 51.6 g (0.24 mol), sodium hydroxide 48 g (1.20 mol) and methanol (270 ml) were added to a 600 ml Hastelloy C Parr bomb equipped with a mechanical stirrer. The bomb was sealed, heated and stirred for 12 hr at 155°C. After cooling, the methanol was removed on a Büchi evaporator. The residue was diluted with dichloromethane and washed with water. The organic extract was dried over anhydrous K_2CO_3, filtered, and the dichloromethane was removed on a Büchi evaporator. The product was distilled at atmospheric pressure, collecting 7.50 g (19%)

of a fraction, bp 215-217°C. Nmr ($CDCl_3$) 1.40 (s, 9, $-C(\underline{CH_3})_3$), 3.85 (s, 3, $-O\underline{CH_3}$), 8.35 (s, 2, H-5,6). Ms m/z: 166 (M^+, calcd for $C_9H_{14}N_2O$: 166).

Hydrolysis of 2-t-Butyl-5-chloropyrimidine (2b)

2-t-Butyl-5-chloropyrimidine (100 g, 0.586 mol) was added to a 2 liter titanium Parr bomb equipped with mechanical stirrer and containing a solution of 95.0 g (1.758 mol) of sodium methoxide in 500 ml of methanol. The bomb was sealed, heated and stirred for 12 h at 165-170°C. The pressure was approximately 280 psig. After cooling, the contents were acidified with anhydrous HCl and filtered and the methanol was evaporated. The residue was diluted with 400 ml of ethyl acetate and placed in the continuous extractor along with 400 ml of water. The solution was extracted for 16 h and the organic phase was separated and analyzed using 1,2,3,4-tetrachlorobenzene as the internal standard. The analyses gave the following: 2-t-butylpyrimidine (1), 3.37%; 2-t-butyl-5-hydroxypyrimidine (4), 100.5%; mass balance, 103.9%. Isolation and recrystallization from carbon tetrachloride gave product (70.51 g, 79%), mp 130-132°C. Ms m/z: 152 (M^+, calcd for $C_8H_{12}N_2O$, 152). Nmr ($CDCl_3$) 1.40 (s, 9, $-C(CH_3)_3$), 8.35 (s, 2, H-5,6), 9.80 (br s, 1, -OH).

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